Pregabalin Orally Disintegrating Tablets

プレガバリン口腔内崩壊錠

Pregabalin Orally Disintegrating Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of pregabalin ($C_8H_{17}NO_2$: 159.23).

Method of preparation Prepare as directed under Tablets, with Pregabalin.

Identification To a quantity of powdered Pregabalin Orally Disintegrating Tablets, equivalent to 25 mg of Pregabalin, add 10 mL of methanol, shake thoroughly, centrifuge, and use the supernatant liquid as the sample solution. Separately, dissolve 10 mg of Pregabalin RS in 4 mL of methanol and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography *<2.03>*. Spot 5 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of methanol, acetonitrile and ammonia solution (28) (65:34:1) to a distance of about 10 cm, and air-dry the plate. Spray evenly a solution of ninhydrin in a mixture of 2-propanol and water (4:1) (1 in 1000) on the plate, and air-dry the plate: the spots obtained from the sample solution and standard solution show the same *R*f value.

Purity Related substances—To a quantity of powdered Pregabalin Orally Disintegrating Tablets, equivalent to 0.1 g of Pregabalin, add the mobile phase A, stir, and add the mobile phase A to make 50 mL. Filter this solution through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the sample solution. Perform the test with 50 μL of the sample solution as directed under Liquid Chromatography *<2.01>* according to the following conditions. Determine each peak area by the automatic integration method and calculate their amounts by the area percentage method: the amount of the peak of related substance A having the relative retention time of about 4.7 to pregabalin is not more than 1.0%, the amount of the peak other than pregabalin and the peak mentioned above is not more than 0.2%, and the total amount of the peaks other than pregabalin and the peak mentioned above is not more than 0.3%. For the area of the peak of the related substance A, multiply the correction factor 0.05.

Operating conditions—

Detector, column, column temperature, mobile phase, flowing of mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay.

Time span of measurement: For 27 minutes after injection, beginning after the solvent peak.

System suitability—

Test for required detectability: To 1 mL of the sample solution, add the mobile phase A to make 100 mL, and use this solution as the solution for system suitability test. Pipet 2 mL of the solution for system suitability test, and add the mobile phase A to make exactly 20 mL. Confirm that the peak area of pregabalin obtained with 50 μL of this solution is equivalent to 7 to 13% of that with 50 μL of the solution for system suitability test.

System performance: When the procedure is run with 50 μL of the solution for system suitability test under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of pregabalin are not less than 3500 and not more than 2.0, respectively.

Uniformity of dosage units *<6.02>* Perform the Mass variation test, or the Content uniformity test according to the following method: it meets the requirement.

To 1 tablet of Pregabalin Orally Disintegrating Tablets, add the mobile phase A, stir, and add the mobile phase A to make exactly V mL so that each mL contains about 0.5 mg of pregabalin ($C_8H_{17}NO_2$). Filter this solution through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the sample solution. Separately, weigh accurately about 25 mg of Pregabalin RS (separately determine the water *<2.48>* in the same manner as Pregabalin), dissolve in the mobile phase A to make exactly 50 mL, and use this solution as the standard solution. Perform the test with exactly 50 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions, and determine the peak areas, A_T and A_S, of pregabalin in each solution.

$$\text{Amount (\%) of pregabalin } (C_8H_{17}NO_2) = M_S \times A_T / A_S \times V / 50$$

M_S: Amount (mg) of Pregabalin RS taken, calculated on the anhydrous basis

Operating conditions—

Proceed as directed in the operating conditions in the Assay.

System suitability—

System performance: When the procedure is run with 50 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of pregabalin are not less than 3500 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 50 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of pregabalin is not more than 1.0%.

Disintegration Being specified separately when the drug is granted approval based on the Law.

Dissolution <*6.10*> When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of water as the dissolution medium, the dissolution rate in 15 minutes of Pregabalin Orally Disintegrating Tablets is not less than 85%.

Start the test with 1 tablet of Pregabalin Orally Disintegrating Tablets, withdraw not less than 10 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 3 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add the dissolution medium to make exactly *V'* mL so that each mL contains about 28 μg of pregabalin ($C_8H_{17}NO_2$), and use this solution as the sample solution. Separately, weigh accurately about 28 mg of Pregabalin RS (separately determine the water <*2.48*> in the same manner as Pregabalin), and dissolve in the dissolution medium to make exactly 100 mL. Pipet 5 mL of this solution, add the dissolution medium to make exactly 50 mL, and use this solution as the standard solution. Perform the test with exactly 50 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, A_T and A_S, of pregabalin in each solution.

Dissolution rate (%) with respect to the labeled amount of pregabalin ($C_8H_{17}NO_2$)

$$= M_S \times A_T / A_S \times V' / V \times 1 / C \times 90$$

M_S: Amount (mg) of Pregabalin RS taken, calculated on the anhydrous basis

C: Labeled amount (mg) of pregabalin ($C_8H_{17}NO_2$) in1 tablet

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with cyanopropylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35℃.

Mobile phase: Dissolve 9.41 g of sodium 1-hexane sulfonate and 2 mL of triethylamine in 880 mL of water, and adjust to pH 3.1 with phosphoric acid. To this solution add 130 mL of acetonitrile for liquid chromatography.

Flow rate: Adjust so that the retention time of pregabalin is about 6 minutes.

System suitability—

System performance: When the procedure is run with 50 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of pregabalin are not less than 5000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 50 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of pregabalin is not more than 2.0%.

Assay Weigh accurately not less than 20 Pregabalin Orally Disintegrating Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 0.15 g of pregabalin ($C_8H_{17}NO_2$), add the mobile phase A, stir, and add the mobile phase A to make exactly 200 mL. Filter this solution through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 10 mL of the filtrate, and use the subsequent filtrate as the sample solution. Separately, weigh accurately about 25 mg of Pregabalin RS (separately determine the water <*2.48*> in the same manner as Pregabalin), and dissolve in the mobile phase A to make exactly 25 mL, and use this solution as the standard solution. Perform the test with exactly 50 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, A_T and A_S, of pregabalin in each solution.

Amount (mg) of pregabalin ($C_8H_{17}NO_2$)

$$= M_S \times A_T / A_S \times 8$$

M_S: Amount (mg) of Pregabalin RS taken, calculated on the anhydrous basis

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3.5 μm in particle diameter).

Column temperature: A constant temperature of about 25℃.

Mobile phase A: Dissolve 2.6 g of potassium dihydrogen phosphate and 1.4 g of dipotassium hydrogen phosphate in 1000 mL of water.

Mobile phase B: Acetonitrile for liquid chromatography

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 － 10	99	1
10 － 15	99 → 75	1 → 25
15 － 27	75	25

Flow rate: 1.0 mL per minute.

System suitability—

System performance: When the procedure is run with 50 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry

factor of the peak of pregabalin are not less than 3500 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 50 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of pregabalin is not more than 1.0%.

Containers and storage Containers—Tight containers.

Others

Related substance A : Refer to it described in Pregabalin.

Add the following to 9.01 Reference Standards section (1):

Pregabalin RS